

IX. CONTROLLED-RELEASE DOSAGE FORMS

A. Introduction

1. Controlled-release dosage forms (also known as delayed-release, sustained-action, prolonged-action, sustained-release, prolonged-release, timed-release, slow-release, extended-action, and extended-release forms) are designed to release drug substance slowly for prolonged action in the body.

2. Controlled-release forms have the following advantages:

- a. Reduction of problems with patient compliance
- b. Employment of less total drug
- c. Minimization or elimination of local or systemic side effects
- d. Minimization of drug accumulation (with chronic dosage)
- e. Reduction of potentiation or loss of drug activity (with chronic use)
- f. Improvement in treatment efficiency
- g. Improvement in speed of control of condition
- h. Reduction in drug level fluctuation
- i. Improvement in bioavailability for some drugs
- j. Improvement in ability to provide special effects (e.g., morning relief of arthritis by bed-time dosing)
- k. Reduction in cost

B. Sustained-release forms. The wide variety of sustained-release forms available can be grouped by the pharmaceutical mechanism employed to provide controlled release.

1. Coated beads or granules produce a blood-level profile similar to that obtained with multiple dosing:

a. A solution of the drug substance in a nonaqueous solvent (such as alcohol) is coated onto small, inert beads or granules made of a combination of sugar and starch. (When the drug dose is large, the starting granules may be composed of the drug itself.)

b. Some of the beads or granules are left uncoated, to provide an immediate release of the drug.

c. Coats of a lipid material (such as beeswax) or a cellulosic material (such as ethylcellulose) are applied to the remainder of the granules, with some granules receiving few coats and some granules many.

d. The various coating thicknesses produce a sustained-release effect.

e. Examples of coated bead or granule dosage forms include Theo-Dur Sprinkle (Key), Spanules (Smith Kline & French), and Sequels (Lederle).

2. Microencapsulation is a process by which solids, liquids, or even gases are encapsulated into microscopic particles by formation of thin coatings of a "wall" material around the substance to be encapsulated.

a. The most common method of microencapsulation is coacervation, which involves addition of a hydrophilic substance to a colloidal drug dispersion.

b. The hydrophilic substance, which acts as the coating material, may be selected from a wide variety of natural and synthetic polymers, including shellacs, waxes, gelatin, starches, cellulose acetate phthalate, ethylcellulose, and others.

c. Once the coating material dissolves, all the drug inside the microcapsule is immediately available for dissolution and absorption. Wall thickness can be varied from less than 1 to 200 μm by changing the amount of the coating material (3% to 30% of total weight).

d. An example of a microencapsulated dosage form is Measurin (Winthrop).

3. Matrix devices may employ insoluble plastics (e.g., polyethylene, polyvinyl acetate, or polymethacrylate), hydrophilic polymers (e.g., methylcellulose or hydroxypropyl methylcellulose), or fatty compounds (e.g., various waxes or glyceryl tristearate).

a. The most common method of preparation is mixing of the drug with the matrix material followed by compression of the material into tablets.

b. The primary dose (the portion of the drug to be released immediately) is placed on the tablet as a layer or coat.

c. The remainder of the dose is released slowly from the matrix.

d. Examples include Gradumet (Abbott), Lonatabs (Geigy), Dospan (Merrell Dow), and Slow-K (Ciba).

4. Osmotic systems include the Oros system, an oral osmotic pump composed of a core tablet and a semipermeable coating with a 0.4-mm diameter hole (produced by a laser beam) for drug exit.

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